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The influence of physical and mental health symptoms on Veterans' functional health status

Tong Sheng, PhD;[1–2*] J. Kaci Fairchild, PhD;[1–2] Jennifer Y. Kong, MSW;[3] Lisa M. Kinoshita, PhD;[1] Jauhtai J. Cheng, MD;[1–2] Jerome A. Yesavage, MD;[1–2] Drew A. Helmer, MD, MS;[4] Matthew J. Reinhard, PsyD;[5] J. Wesson Ashford, MD, PhD;[1–2] Maheen M. Adamson, PhD[1–2,6]

[1]War Related Illness and Injury Study Center, Department of Veterans Affairs (VA) Palo Alto Health Care System, Palo Alto, CA; [2]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA; [3]School of Social Work, Boston University, Boston, MA; [4]War Related Illness and Injury Study Center, VA New Jersey Health Care System, East Orange, NJ; [5]War Related Illness and Injury Study Center, VA Medical Center, Washington DC; [6]Defense and Veterans Brain Injury Center, VA Palo Alto Health Care System, Palo Alto, CA

Abstract—Veterans who have been deployed to combat often have complex medical histories, including some combination of traumatic brain injury (TBI); mental health problems; and other chronic, medically unexplained symptoms (i.e., chronic multisymptom illness [CMI] clusters). How these multiple pathologies relate to functional health is unclear. In the current study, 120 Veterans (across multiple combat cohorts) underwent comprehensive clinical evaluations and completed self-report assessments of mental health symptoms (Patient Health Questionnaire-2 [PHQ-2], Posttraumatic Stress Disorder Checklist–Civilian Version [PCL-C]) and functional health (Veterans Rand 36-Item Health Survey). Canonical correlation and regression modeling using split-sample permutation tests revealed that the PHQ-2/PCL-C composite variable (among TBI severity and number of problematic CMI clusters) was the primary predictor of multiple functional health domains. Two subscales, Bodily Pain and General Health, were associated with multiple predictors (TBI, PHQ-2/PCL-C, and CMI; and PHQ-2/PCL-C and CMI, respectively), demonstrating the multifaceted nature of how distinct medical problems might uniquely and collectively impair aspects of functional health. Apart from these findings, however, TBI and CMI were not predictors of any other aspects of functional health. Taken together, our findings suggest that mental health problems might exert ubiquitous influence over multiple domains of functional health. Thus, screening of mental health problems and education and promotion of mental health resources can be important to the treatment and care of Veterans.

Key words: chronic multisymptom illness, daily functioning, functional health, mental health, posttraumatic stress, quality of life, symptoms, traumatic brain injury, Veterans, war-related illness.

INTRODUCTION

Veterans who have been deployed to combat often exhibit many physical and mental health symptoms as a consequence of their experiences in service. However, how these multiple war-related illnesses affect Veterans'

Abbreviations: CMI = chronic multisymptom illness, OEF = Operation Enduring Freedom, OIF = Operation Iraqi Freedom, OND = Operation New Dawn, PCL-C = Posttraumatic Stress Disorder Checklist–Civilian Version, PHQ-2 = Patient Health Questionnaire-2, PTSD = posttraumatic stress disorder, TBI = traumatic brain injury, VA = Department of Veterans Affairs, VR-36 = Veterans RAND 36-Item Health Survey, WRIISC = War Related Illness and Injury Study Center.

***Address all correspondence to Tong Sheng, PhD; 3801 Miranda Ave, Palo Alto, CA 94303; 650-493-5000, ext 67238. Email: Tong.Sheng@va.gov**

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functional health and health-related quality of life is currently not well understood. The California campus of the War Related Illness and Injury Study Center (WRIISC) at the Department of Veterans Affairs (VA) Palo Alto Health Care System is one of three WRIISC sites nationwide (including East Orange, New Jersey, and Washington, DC) that focus on the postdeployment health concerns of Veterans by providing consultation services as part of a national effort to provide clinical care to Veterans with complex health problems [1].

Some Veteran patients are eligible to be referred to the WRIISC program by their local VA providers to seek a second opinion on their conditions, such as those who have complex health conditions and medically unexplained symptoms, show little to no symptom improvement following several tests and/or treatment or follow-up, or have possible service-related problems or concerns related to environmental exposures. (For referral and enrollment information, see http://www.warrelatedillness.va.gov/WARRELATEDILLNESS/referral/.) As such, the WRIISC program evaluates Veterans who served in all combat eras from the Vietnam War to Operation Iraqi Freedom/Operation Enduring Freedom/Operation New Dawn (OIF/OEF/OND). Enrolled Veterans are brought to the designated service-area WRIISC site for a multiday assessment, during which they are evaluated by a specialized team of clinicians, researchers, and educators who offer recommendations for further testing and treatment.

Typical WRIISC patients have a complex medical history with problems related to the chronic sequelae of traumatic brain injury (TBI), mental health disorders (e.g., depression, posttraumatic stress disorder [PTSD]), and other chronic medical conditions that involve multiple symptoms without clear explanations. These chronic, medically unexplained cases span multiple domains (i.e., clusters), including fatigue; pain; problems in pulmonary, dermatologic, and gastrointestinal systems; and problems with sleep, mood, cognition, and memory [2–3]. These cases, collectively described as *chronic multisymptom illness* (CMI), are frequently observed among Veterans who have served in the Gulf War [4]. However, in more recent reports, CMI-like cases are also described in Veterans deployed to other conflicts (e.g., OIF/OEF/OND) as well as in nondeployed Veterans [5–6].

WRIISC patients are more likely to exhibit TBI, mental health problems, and problems in CMI symptom clusters at higher rates than are epidemiological Veteran samples because patients are referred to the WRIISC program specifically because they presented chronic and complex medical problems. In representative Veteran samples, TBI is observed in an estimated 10 to 30 percent of Veterans [7–8]. Similar proportions are reported for depression (14%; National Alliance on Mental Illness; http://www.nami.org) and PTSD (4–20% in Gulf War-era and OIF/OEF/OND Veteran samples) [9–11]. Estimated numbers of Veterans affected by CMI are more variable because of multiple working case definitions. Nonetheless, an estimated 8 to 62 percent of Gulf War-era Veteran samples are thought to be affected by CMI problems [3–4]. The higher rates of TBI, mental health problems, CMI problems, and comorbidities in WRIISC patients introduce an analytical challenge and potentially obfuscate comparisons with studies involving other Veteran cohorts (e.g., the Vietnam War, Gulf War, and OIF/OEF/OND conflict eras [12–16]). However, such patients provide a unique opportunity to gain insights into the potential effect that multiple medical problems and comorbidities might have on other health outcomes.

Because postdeployed Veterans typically experience some combination of TBI, mental health, and CMI symptoms, a better understanding of how multiple medical factors are potentially associated with impaired functional health and health-related quality of life may inform more effective treatment approaches [16–21]. Whereas contemporary medical practice generally treats individual medical conditions independently from comorbidities, different pathologies can have overlapping or compounding effects. Thus, a more integrated treatment approach addressing multiple aspects of a Veteran's health might be more beneficial. In the current study, we aimed to characterize the extent to which commonly observed war-related pathologies (i.e., TBI, depression, PTSD, and problems in CMI clusters) were associated with various aspects of functional health and health-related quality of life in Veterans evaluated at the California WRIISC program.

We expected different domains of functional health to be uniquely associated with different medical factors. For example, TBI and problems in CMI symptom clusters were expected to be more strongly associated with physical, bodily, and pain-related impairments (e.g., limited ability in moderate and intense physical activities, difficulty in performing work, limitations as a result of severe pain), whereas mental health symptoms related to depression and PTSD might be more strongly associated with psychological, emotional, and social impairments (e.g., limitations from feeling low energy and anxious, limitations in social activities). However, the relationships between medical factors and functional health might be substantially more complex, with multiple medical factors (TBI, depression, PTSD, problems in CMI clusters) influencing various aspects of functional health. Thus, the current investigation represented a preliminary effort toward elucidating these relationships in a Veteran sample characterized by multiple comorbid pathologies.

METHODS

Sample

Participants in this study (*N* = 120; mean age, 47.8 yr, range 27–78 yr; 15 females) were Veterans seen at the California WRIISC. They are a sample of patients evaluated at the WRIISC program who met the following criteria: (1) completed a self-report questionnaire packet assessing demographic and health-related information, (2) underwent the comprehensive on-site clinical evaluation, and (3) gave written consent to making their data available for research purposes.

The Veterans included in the study were part of a mixed cohort sample, the majority of whom had served in combat. Most Veterans had been deployed to the Gulf War (46%), but a substantial proportion had been deployed to OIF/OEF/OND (38%). Smaller groups were deployed to the Vietnam War (14%) and other conflicts (6%). Fifteen percent have been deployed to multiple combat theaters, and 6 percent have never been deployed. This small number of nondeployed Veterans demonstrates the fact that chronic illnesses and injuries can also be incurred from training-related activities and exposures outside of combat. Although the WRIISC programs typically treat combat Veterans, the programs also receive and enroll referrals involving noncombat Veterans who present persistent complex symptoms. For sample characteristics, see **Table 1** and the **Figure**.

Clinical Assessments and Determination of Clinical Conditions

Neurological Examination for Assessment of Traumatic Brain Injury

All patients included in the study underwent a complete neurological examination by a neurologist for the assessment of TBI. Each patient was examined and diagnosed

Table 1.
Complete demographic and medical history information for the Veterans evaluated in the California WRIISC program (*N* = 120).

Demographic*	Description
Age, yr (range)	47.8 (27–78)
Education, yr (mean ± SD)	14.3 ± 3.5
Sex, Female, %	12.5
Combat History/Theater, %	
Vietnam	14.2
GW1	45.8
OIF/OEF/OND	38.3
Other	5.8
No. Deployments, %	
0	5.8
1	79.2
2+	15.0
Medical History, %	
TBI Diagnosis†	57.5
None	42.5
Mild	52.5
Moderate/Severe	5.0
Probable Depression‡	59.2
PTSD Diagnosis†	65.0
Affected CMI Clusters, %§	
Pain	95.8
Sleep	85.8
Gastrointestinal	60.0
Cognitive NOS	55.8
Fatigue	49.2
Dermatologic	34.3
Pulmonary	24.2
Problematic CMI Clusters, No. (cumulative %)	
0	3.3 (100.0)
1	1.7 (96.7)
2	5.0 (95.0)
3	23.3 (90.0)
4	29.2 (66.7)
5	21.7 (37.5)
6	12.5 (15.8)
7	3.3 (3.3)

*Demographic and combat history information were collected from Veterans during intake into the California WRIISC program.
†Diagnoses of TBI and PTSD were made by the staff neurologist, clinical psychologist, and psychiatrist.
‡Likelihood of depression was based on the self-report screening measurement Patient Health Questionnaire-2, using a cutoff of 3.
§Diagnoses of problems in CMI symptom clusters were made by providers at other various specialty clinics.
CMI = chronic multisymptom illness, GW1 = Gulf War 1, No. = number, NOS = not otherwise specified, OEF = Operation Enduring Freedom, OIF = Operation Iraqi Freedom, OND = Operation New Dawn, PTSD = posttraumatic stress disorder, SD = standard deviation, TBI = traumatic brain injury, WRIISC = War Related Illness and Injury Study Center.

Table 1.
Complete demographic and medical history information for the Veterans evaluated in the California WRIISC program (*N* = 120).

(with determination of severity) in accordance with the guidelines set forth by the VA and the Department of Defense [22–23]. A TBI was defined as any period of loss or

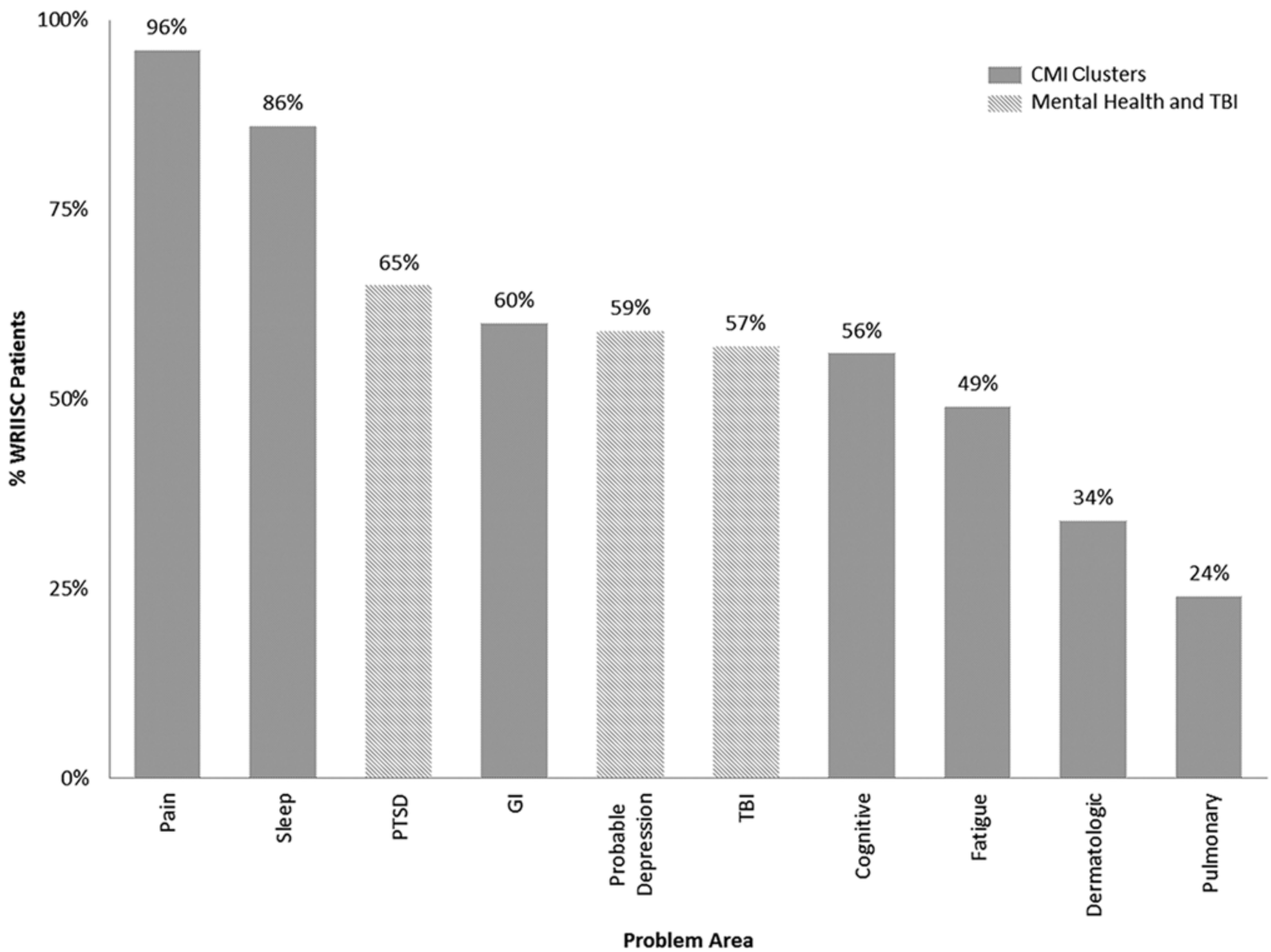

Figure.
War Related Illness and Injury Study Center (WRIISC) at the Department of Veterans Affairs (VA) Palo Alto Health Care System provides consultation for patients with complex medical problems. Common among these Veterans are traumatic brain injury (TBI), posttraumatic stress disorder (PTSD), probable depression, and problems in chronic multisymptom illness (CMI) clusters. Shown are the percentages of individuals seen at the VA Palo Alto WRIISC reporting symptoms in CMI clusters and mental health and TBI problem areas. GI = gastrointestinal.

decreased level of consciousness, any loss of memory immediately prior to or following injury, any alteration in mental state (e.g., confusion, disorientation, slowed thinking), neurological deficits (e.g., weakness, loss of balance, loss in vision or other senses, aphasia), or intracranial lesion as the result of an external force. Although Veterans may have possibly (or even likely) sustained multiple TBIs in the past, the neurologist made all diagnoses based on one self-reported incident at the patient's disclosure. Accurate and reliable diagnosis of TBI was limited because it relied on self-reporting without consistently available supporting documentation or medical information at the time of injury. However, self-reporting and sparse medical records were the only information sources available [24]. Based on the retrospective self-report (corroborated with a chart review of past medical records in the VA's centralized charting system prior to the interview), patients were diagnosed as having no TBI, mild TBI (normal brain scan, loss of consciousness <30 min, altered mental state <24 h, posttraumatic amnesia <1 d), or moderate-severe TBI (normal or abnormal brain scan, loss of consciousness >30 min, altered mental state >24 h, posttraumatic amnesia >1 d).

Assessment of Chronic Multisymptom Illness

Veterans' CMI symptom profiles were characterized by noting active problems within individual CMI clusters. A chart review of patients' on-site evaluations was performed via the VA's Computerized Patient Record System, and current diagnoses in the following clusters were noted: pain, fatigue, dermatologic, gastrointestinal, pulmonary, sleep, and cognitive disorders not otherwise specified. Only diagnoses charted during the patients' WRIISC evaluations were included in this study. A CMI symptom cluster was considered *problematic* if one or more medical conditions within the cluster were noted by a provider. Cognitive disorders not otherwise specified were diagnosed by consensus of the psychiatrist, neurologist, and clinical psychologist. The total number of unique problematic CMI clusters was tallied for each patient.

Self-Report Measures

Probable Depression

Patients completed the Patient Health Questionnaire-2 (PHQ-2), a brief, two-item measure that screens for symptoms of depression. It was shown to have acceptable sensitivity (83%–100%) and specificity (77%–92%) for major depression in civilian and Veteran samples and is routinely used in the VA as part of the Primary Care Manual [25–27].

Posttraumatic Stress

Patients completed the PTSD Checklist–Civilian Version (PCL-C), a 17-item self-report measure that assesses severity of symptoms resulting from stressful life experiences (not restricted to military-specific trauma) across different symptom domains of PTSD (re-experiencing, avoidance, and hyper arousal; criteria from the Diagnostic and Statistical Manual of Mental Disorders-4th Edition) [28–29]. The sum of all 17 responses was used as an indicator of global PTSD symptom severity. Psychometric properties of the PCL-C have been reported as favorable, with good test-retest reliability (>0.75), internal consistency (>0.83), and strong correlation with clinical standards [29–30].

Functional Health Outcomes

The Veterans RAND 36-Item Health Survey (VR-36) was administered to assess constructs affecting health-related quality of life. The VR-36 is a 36-item, Veteran-specific inventory based on the functional health measure 36-Item Short Form Survey [31–33]. The VR-36 assesses different aspects of functioning and well-being across eight subscales (domains): Physical Functioning, Role Limitations: Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations: Emotional, and Mental Health. Descriptions and sample items of each subscale are presented in **Table 2**. These Likert-style items were computed into summary scores for each domain (scaled 0–100), with greater scores indicating better functioning. Internal reliability is generally good, with seven of the eight individual domains having Cronbach alpha between 0.76 and 0.91 [34].

Predictors of Functional Health Outcomes

To quantify the associations between medical factors (TBI severity, PHQ-2, PCL-C, and number of problematic CMI clusters) and functional health measures (the eight VR-36 subscales), we performed primary analyses to observe the overall multivariate relationship between medical factors and functional health measures, followed by confirmatory regression modeling and cross-validation using split-sample permutation tests.

Data Transformation

Prior to data analyses, we inspected all self-report measures for outliers. Outlier detection was performed using the Tukey procedure on the PHQ-2, PCL-C, and VR-36. Outliers were defined as >1.5 times the interquartile range beyond the first and third quartiles. No outliers were identified based on the PHQ-2 and PCL-C, but four patients were flagged as potential outliers among the eight VR-36 subscales. On further inspection, however, we found that distributions of many of the VR-36 subscales were positively skewed (overall tendency to report lower scores on nearly all subscales; **Table 2**. Because our sample was expected to exhibit greater disability in functional health, rather than exclude the flagged patients with lower subscale scores as outliers, we transformed all VR-36 subscales scores using Box-Cox transformations to give each subscale a more normal distribution.

In addition, because we expected depression and PTSD to be correlated, we combined the PHQ-2 and PCL-C scores to form a mental health composite (by summing the *z*-transforms of the two) [35–36]. Inclusion of collinear terms in regression modeling would have negatively influenced interpretation of results and reduced statistical power. Thus, although we were unable to distinguish the relative contributions of depression and PTSD symptoms

Table 2.
Descriptions of self-report measures an overall sample mean ± standard deviation (n = 120).

Measurement	Description	Sample Items	Mean ± Standard Deviation
PHQ-2 (2 items)	Frequency of depressed mood and anhedonia over the past 2 wk	Little interest or pleasure in doing things? Feeling down, depressed, or hopeless?	3.2 ± 2.1
PCL-C (17 items)	DSM-IV symptoms of PTSD	Repeated, disturbing memories, thoughts, or images of a stressful experience from the past? Avoid activities or situations because they remind you of a stressful experience from the past? Feeling irritable or having angry outbursts?	52.5 ± 17.9
VR-36	Health-related quality of life, disease burden, and effect on daily functioning	—	—
Physical Functioning (9 items)	Limitations in range of physical activities	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? Walking several blocks?	41.7 ± 26.4
Role Limitations: Physical (5 items)	Limitations in performing daily activities because of physical problems	Had difficulty performing the work or other activities (for example, it took extra effort)? Were limited in the kind of work or other activities?	24.9 ± 25.7
Bodily Pain (2 items)	Intensity of pain and extent to which pain interferes with daily activities	During the past 4 wk, how much did pain interfere with your normal work (including both work outside the home and housework)?	26.3± 22.9
General Health (4 items)	Perception of general health	In general, would you say your health is [poor–excellent]? Compared to one year ago, how would you rate your health in general now?	29.1 ± 19.0
Vitality (4 items)	Subjective rating of energy and fatigue	Did you have a lot of energy? Did you feel worn out?	20.3 ± 19.9
Social Functioning (1 item)	Limitations in social activities	During the past 4 wk, to what extent have your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	26.6 ± 22.9
Role Limitations: Emotional (3 items)	Limitations in performing daily activities due to emotional problems	Didn't do work or other activities as carefully as usual? Accomplished less than you would like?	48.8 ± 33.5
Mental Health (5 items)	Subjective rating of mental health and emotional well-being	Have you been a very nervous person? Have you felt so down in the dumps that nothing could cheer you up?	47.9 ± 24.6

Note: Raw VR-36 scores are described prior to Box-Cox transformation.
DSM–IV = Diagnostic and Statistical Manual of Mental Disorders-4th Edition, PCL-C = Posttraumatic Stress Disorder Checklist–Civilian Version, PHQ-2 = Patient Health Questionnaire-2, PTSD = posttraumatic stress disorder, VR-36 = Veterans RAND 36-Item Health Survey.

to functional health, the use of a PHQ-2/PCL-C composite variable allowed us to investigate the potential effects of a broader mental health construct.

Primary Analyses

Our primary objective was to describe potential relationships between medical factors and multiple functional health domains, so we performed a series of multivariate and multiple regression analyses.

Canonical correlation analysis. To gain an appreciation of the overall relationship between medical factors and functional health measures, we performed a canonical correlation analysis with TBI severity, PHQ-2/PCL-C composite, and number of problematic CMI clusters as predictor variables, and the eight subscales of the VR-36 as outcome variables.

Split-sample permutation testing and cross-validation of multiple regression models. To quantify specific associations between medical factors and functional health measures (especially those indicated by the canonical correlation analysis), we tested standard regression models using split-sample permutation tests and cross-validation. Permutation tests using split samples offered several analytic advantages: precise estimates of effect sizes and interquartile ranges, insights into the overall distributions of effects, and metrics of generalizability based on cross-validations between the tested (discovery) and withheld (generalizability) subsamples.

The sample of 120 subjects was split into two randomly selected groups of 60 across 10,000 iterations. During each iterative process, for each VR-36 subscale, a standard linear regression model with medical factors and demographic variables (age and education) as predictor variables and the VR-36 subscale scores as the outcome variables was tested using the discovery subsample. Regression coefficients from the discovery model were then applied to the generalizability subsample data to obtain predicted VR-36 subscale scores. Cross-validation reliability was quantified as a Pearson correlation between the predicted and actual subscale scores in the generalizability subsample. After 10,000 iterations, distributions of the overall model fit (adjusted R^2) and its cross-validation (R) were obtained for each VR-36 subscale.

Contribution of individual medical factors to functional outcomes. Using permutation tests, we also computed distributions of estimated effect sizes (beta, t-statistic) for each regression coefficient (i.e., for each medical factor, accounting for age and education as covariates), for each VR-36 subscale. By examining these distributions, we inferred the relative importance of each medical factor to each functional health domain.

Secondary Analyses

The medical factor variables in the primary analyses varied in form, so we ruled out potential effects of variable structure on the medical factor/functional outcome relationships by performing the same analyses on binary forms of the medical factor variables. Medical factors were binarized as follows: TBI severity (no TBI versus mild TBI; moderate-severe TBI cases were excluded from this analysis because of potential construct heterogeneity if combined with mild TBI cases), PHQ-2 (using a cutoff of 3+), PCL-C (using a cutoff of 55+), and CMI variables (using a median split of 4+ symptom clusters) [25,27,37–38]. The cutoff points for the PHQ-2 and PCL-C were chosen because the WRIISC Veteran sample had more complex medical histories than those reported in typical Veteran samples.

We also performed post hoc zero-order correlation analyses between each medical factor and each VR-36 subscale to observe relative associations without regressing out the potential influences of the other medical factors or demographic variables.

Although we considered depression and PTSD symptoms jointly in the primary analyses because of potential collinearity issues, we also carried out the same canonical correlation and split-sample permutation modeling analyses while considering PHQ-2 and PCL-C independently.

We had hoped to gain a more nuanced understanding of potential medical factor/functional health domain relationships through these secondary analyses, but because these analyses are exploratory we have refrained from discussing them in detail in this article.

RESULTS

Medical History and Self-Report Measures

More than half of California WRIISC Veterans met diagnostic criteria for mild (52.5%) or moderate TBI (5%). An even larger proportion met diagnostic criteria for PTSD (65%). Nearly all (97%) reported problems from at least one CMI symptom cluster; two-thirds had problems in four or more unique CMI symptom clusters. Complete demographic and medical history information are shown in **Table 1**.

Mean response on the PHQ-2 was 3.2, and the mean response on the PCL-C was 52.5. Mean raw scores on VR-36 subscales ranged from 20.3 to 48.8. Descriptive data for all self-report measures are shown in **Table 2**.

Primary Analyses

Canonical Correlation Analysis Results

A significant relationship was observed between the first canonical variate pair (Wilks lambda = 0.24, $F = 8.43$, $p < 0.001$). The pooled squared canonical correlation for the first canonical pair was 0.88. In the first canonical root, the PHQ-2/PCL-C composite was the most important (standardized canonical coefficient = 0.53) among predictor variables, and Mental Health (standardized canonical coefficient = –0.61), Role Limitations: Emotional (stan-

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dardized canonical coefficient = –0.37), and Social Functioning (standardized canonical coefficient = –0.20) were the most important among outcome variables. All canonical correlation results are presented in **Table 3**.

Split-Sample Permutation Tests and Cross-Validation

Split-sample permutation tests of regression models predicting VR-36 subscale scores indicated that the Mental Health, Role Limitations: Emotional, and Social Functioning subscales were substantially accounted for by the medical factors and covariates (mean adjusted R^2 = 0.61, 0.52, 0.26, respectively). The Bodily Pain, Vitality, and General Health subscales were also well modeled by medical factors and covariates to lesser extents (mean adjusted R^2 = 0.19, 0.14, 0.13, respectively). The Physical Functioning and Role Limitations: Physical subscales were not well explained by the medical factors included in the analyses. All split-sample permutation test results and 95 percent interquartile ranges are shown in **Table 4**.

The Mental Health, Role Limitations: Emotional, and Social Functioning subscales also had the highest cross-validation reliability (adjusted mean R = 0.78, 0.71, 0.48, respectively). The Bodily Pain, Vitality, General Health, and Physical Functioning subscales had slightly lower cross-validation reliability (mean adjusted R = 0.40, 0.31, 0.30, 0.25, respectively). Only the Role Limitations: Physical subscale had cross-validation reliability close to zero. All cross-validation results and 95 percent interquartile ranges are shown in **Table 4**.

Table 3.
Canonical correlation results. In bold: significant canonical pairs ($p < 0.05$).

Variables	Canonical Roots		
	1	2	3
Independent			
TBI Severity	**0.016**	0.772	–0.675
PHQ-2/PCL-C Composite*	**0.533**	–0.173	–0.014
No. CMI Clusters	**0.069**	0.611	0.808
Dependent			
Physical Functioning	**–0.070**	0.007	0.445
Mental Health†	**–0.607**	0.356	0.229
Vitality	**0.018**	0.377	–0.098
Social Functioning†	**–0.203**	0.064	–0.889
Bodily Pain	**–0.031**	–1.150	0.342
General Health	**0.014**	–0.426	–0.749
Role Limitations: Physical	**0.143**	0.285	0.234
Role Limitations: Emotional†	**–0.369**	0.087	0.353
R	**0.846**	0.349	0.204
Wilks Lambda	**0.238**	0.842	0.958
F	**8.435**	1.414	0.806
p	**<0.001**	0.145	0.526
df1	**24.000**	16.000	6.000
df2	**316.730**	220.000	111.000

Table 3.
Canonical correlation results. In bold: significant canonical pairs ($p < 0.05$).

*The most important among independent variables.
†The most important among dependent variables.
CMI = chronic multisysptom illness, No. = number, PHQ-2/PCL-C = Patient Health Questionnaire-2/Posttraumatic Stress Disorder Checklist–Civilian Version, TBI = traumatic brain injury.

Contribution of Individual Medical Factors to Functional Outcomes

Taking into account age, education, and the other medical factors, we found that the PHQ-2/PCL-C composite had the strongest association with all eight VR-36 subscales. In contrast, TBI severity and number of problematic CMI symptom clusters showed little or no associations at all. Both TBI severity and number of problematic CMI clusters were associated with the Bodily Pain subscale, and the number of problematic CMI clusters was also associated with the General Health subscale. Described in a different way, the Mental Health (t = –9.17), Role Limitations: Emotional (t = –7.58), Social Functioning (t = –4.06), Vitality (t = –2.91), Physical Functioning (t = –2.20), and Role Limitations: Physical (t = –1.62) subscales were predicted by the PHQ-2/PCL-C composite alone, and the General Health subscale was predicted by PHQ-2/PCL-C and the number of problematic CMI clusters (t = –2.49, –1.50, respectively). The Bodily Pain subscale was predicted by the triad of TBI severity, PHQ-2/PCL-C, and number of problematic CMI clusters (t = –1.90, –2.20, –1.41, respectively). All regression coefficients and 95 percent confidence interquartile ranges for all medical factors for all VR-36 subscales are shown in **Table 5**.

Secondary Analyses

Secondary analyses assessing potential effects of variable structure and zero-order correlations were largely similar to the findings described previously.

Table 4.
Results of standard multiple regression models quantifying associations between medical factors and functional health outcomes. In bold: 95 percent interquartile ranges (IQRs) that do not span zero for both overall model fit and cross-validation performance and corresponding columns.

Functional Health Outcomes	Overall Model Fit (Adjusted R^2)	95% IQR	Cross-Validation Performance (R)	95% IQR
Mental Health	**0.612**	**0.474 to 0.737**	**0.775**	**0.692 to 0.852**
Role Limitations: Emotional	**0.524**	**0.402 to 0.640**	**0.708**	**0.619 to 0.786**
Social Functioning	**0.257**	**0.110 to 0.423**	**0.479**	**0.330 to 0.607**
Bodily Pain	**0.188**	**0.047 to 0.351**	**0.402**	**0.244 to 0.545**
Vitality	**0.138**	**0.003 to 0.306**	**0.311**	**0.133 to 0.475**
General Health	**0.128**	**0.001 to 0.268**	**0.303**	**0.126 to 0.456**
Physical Functioning	0.089	–0.027 to 0.237	0.250	0.063 to 0.409
Role Limitations: Physical	0.026	–0.065 to 0.162	0.105	–0.105 to 0.279

Note: Permutation tests were performed based on N = 120 patients split into two groups, discovery (n = 60) and generalizability (n = 60), over 10,000 iterations.

Table 5.
Effect of individual medical factors on functional health outcomes (*t*-statistic and 95% interquartile range [IQR]). In bold: 95 percent IQRs that do not span zero and corresponding columns.

Medical Factors	TBI Severity	95% IQR	PHQ-2/PCL-C Composite	95% IQR	No. CMI	95% IQR
Mental Health	0.263	–1.063 to 1.678	**–9.171**	**–12.093 to –6.797**	–0.275	–1.569 to 1.063
Role Limitations: Emotional	–0.451	–1.976 to 1.007	**–7.581**	**–9.619 to –5.817**	–0.377	–1.794 to 0.981
Social Functioning	0.076	–1.286 to 1.461	**–4.065**	**–5.976 to –2.410**	–1.248	–2.627 to 0.127
Bodily Pain	**–1.903**	**–3.422 to –0.497**	**–2.196**	**–3.775 to –0.756**	**–1.412**	**–2.811 to –0.047**
Vitality	0.243	–1.142 to 1.608	**–2.914**	**–4.634 to –1.412**	–0.455	–1.872 to 0.945
General Health	–0.143	–1.645 to 1.317	**–2.490**	**–4.175 to –0.870**	**–1.502**	**–2.929 to –0.117**
Physical Functioning	–0.780	–2.120 to 0.483	**–2.204**	**–3.752 to –0.738**	–0.558	–2.097 to 0.970
Role Limitations: Physical	–0.305	–1.798 to 1.142	**–1.620**	**–3.284 to –0.082**	–0.352	–1.674 to 0.983

Note: Results of standard multiple regression models quantifying the associations between medical (TBI severity, PHQ-2/PCL-C composite, and number of problematic CMI clusters) and demographic factors (age, years of education) and various daily function domains. Effects of individual medical factors (TBI severity, PHQ-2/PCL-C composite, number of problematic CMI clusters) are shown, accounted for demographic factors (age and education) and all other medical factors. Permutation tests were performed based on N = 120 patients split into two groups, discovery (n = 60) and generalizability (n = 60), over 10,000 iterations.
CMI = chronic multisymptom illness, No. = number, PHQ-2/PCL-C = Patient Health Questionnaire-2/Posttraumatic Stress Disorder Checklist–Civilian Version, TBI = traumatic brain injury.

DISCUSSION

The current investigation considered whether and to what extent war-related illnesses such as TBI, mental health problems, and problems in CMI clusters are associated with multiple domains of functional health/health-related quality of life in a non-cohort-specific Veteran sample marked by complex medical comorbidities. Converging results from canonical correlation and split-sample permutation regression modeling indicate that such medical factors seem to affect a broad range of functional health, with impairments spanning psychological, mood/affect, social, and bodily domains. These findings support and complement previously reported associations between TBI, depression, PTSD, and problems in CMI clusters and functional health outcomes in Gulf War and OIF/OEF Veterans [15,18,39].

For the vast majority of functional health domains, the Mental Health construct captured by the PHQ-2/PCL-C composite variable is the only strong indicator. These findings are consistent with previous reports and confirm the expected relationship between mental health symptoms and psychological, mood/affect, and social aspects of health-related quality of life [13,40–41].

The Bodily Pain subscale, which indexes functional limitations because of physical pain, is strongly associated with TBI severity and number of problematic CMI clusters in addition to PHQ-2/PCL-C. Given the great likelihood of Veterans suffering co-occurring injuries during combat (e.g., co-occurring PTSD following TBI or other bodily injuries), the observation that physical and psychological sources of trauma might jointly manifest as a common form of functional limitation is not surprising. This finding also aligns with previous reports linking TBI, mental health problems, and CMI problems to functional limitations from pain [15,42]. In addition, this finding also demonstrates the multifaceted nature of how distinct medical problems might uniquely and collectively impair specific aspects of functional health.

Similarly, the General Health subscale, which indexes general perceptions and attitudes toward one's health, is strongly associated with both PHQ-2/PCL-C and the number of problematic CMI clusters. This finding is consistent with previous reports and highlights the complementary influences of mental health and physical medical symptoms affecting Veterans' general views toward health and quality of life [13–14,39].

We did not observe associations between TBI severity and seven of the eight VR-36 subscales. This result is somewhat unexpected in light of previous studies involving civilian and OIF/OEF/OND Veteran samples [15,43–44]. Similarly, the lack of associations between CMI status and six of the eight subscales is also surprising given the previously described associations, particularly from Gulf War and general Veteran samples [4,31,45]. One explanation for these discrepancies is that the inclusion of mental health variables in the current analyses potentially obscures precise characterizations of the associations between TBI and CMI and functional health measures. Previous studies have suggested that mental health factors in general, and PTSD in particular, might be a mediator of such relationships [13,15,46–47]. However, post hoc zero-order correlation analyses also fail to show any relationships between TBI/CMI and functional health (with one exception being a small association between TBI severity and the Role Limitations: Emotional subscale). A more likely possibility is that the symptoms and problematic features in TBI and CMI are too specific (e.g., involving memory, cognition, somatic problems) and their operationalization in the current study is too crude, such that their potential relationships with functional health domains are not aptly measured. Indeed, previous studies reporting such associations tend to have larger samples and adopt between-groups study designs that aim to minimize within-group heterogeneity. Also plausible, however, is the idea that physical medical problems such as those stemming from TBI and problems in CMI symptom clusters might simply not be very strong indicators of daily functioning compared to mental health problems. This explanation might be particularly pertinent in a patient sample with psychiatric comorbidities.

Although previous studies have reported associations between different forms of war-related pathologies, we did not observe overwhelming associations between TBI, mental health symptoms, and problems in CMI symptom clusters. Apart from the expected associations between PTSD and depression and between TBI and PTSD, no other associations among medical factors were observed [15–16,19,35–36,48–50]. This result is surprising given the body of Gulf War and OIF/OEF/OND cohort research that shows associations between TBI and CMI and mental health conditions and CMI [17–18,21,51–54]. These discrepancies might result from the differences in variable definition, analytic decision, sample size, or some combination of all of these. On the other hand, the association between TBI and PTSD juxtaposed to the lack of associations between them and CMI problems indicates that the traumatic events and experiences leading to development of TBI and PTSD are likely to be qualitatively similar but distinct from those that cause chronic, medically unexplained symptoms in CMI clusters (e.g., related to exposure to a combination of environmental, biological, and chemical agents) [55–57].

The complex medical problems and high comorbidity rates of California WRIISC Veterans introduce potential limitations on both analytical and inferential fronts. Incidences of TBI, probable depression, PTSD, and problems in CMI clusters are higher in California WRIISC patients than in other epidemiological Veteran samples across multiple conflict eras, limiting comparisons with other studies.

Apart from the complexities introduced by our unique Veteran patient sample, other factors might also limit the inferential power of our findings. In particular, we adopt an integrative approach that brings together a range of clinically derived and self-reported data, which might present analytic challenges.

The clinically derived information (diagnoses of TBI and CMI cluster problems) is somewhat hindering because of its binary and nonparametric nature. As such, we are unable to gain fine-grained insights regarding the severity of patients' clinical status. This limitation stifles our otherwise powerful analytic strategy. In particular, a more thorough documentation of the chronic sequelae of TBI will be more informative. On the other hand, our self-report measures (PHQ-2, PCL-C, VR-36), although more continuous are subject to response bias, response compliance, and deviant responding concerns inherent to self-report instruments.

The split-sample permutation analytic approach with cross-validation, though offering several advantages, is correlational and does not allow causal inferences to be made. Even in the event of very strong associations, the potential causal directionality of such associations cannot be known with certainty without additional longitudinal and intervention research methods. For example, although individuals characterized as having high negative affect are thought to endorse medical symptoms at a higher rate, an equally plausible interpretation is that individuals with more medical symptoms might experience heightened negative affect. Both explanations can be true, and the overall relationship between negative affect and medical pathologies is thought to be bidirectional [58–60].

The context within which the data were collected should also be considered. All clinically derived and self-report data were collected as part of the intake and evaluation process during a multiday clinical visit. The quality of the data was susceptible to patient compliance, patient fatigue, disease burden, and the potential for seeking secondary gains [61]. Without consistent and systematic assessments for effort, fatigue, and compliance, we cannot rule out their potential influences on the data.

CONCLUSIONS

Taken together, our results show that in a Veteran sample characterized by complex medical and psychological problems and multiple comorbidities, mental health symptoms related to depression and PTSD emerge as the prominent factor contributing to impaired health-related quality of life. The strong associations between mental health symptom severity and multiple functional health domains suggest that a stronger emphasis on mental health screening, education, and treatment could lead to improvements in health-related quality of life.

Surprisingly, severity of TBI and number of problematic CMI symptom clusters are not identified as overwhelmingly strong indicators of most aspects of functional health. Even so, TBI and CMI cluster symptoms should not be discounted; they are likely to contribute to other aspects of functional health and quality of life beyond the scope of the current investigation.

Improvements in the definition and operationalization of symptoms related to TBI and CMI problems may yield important clinical and analytical value. For example, more continuous and sensitive descriptions of TBI and CMI symptoms with a broader range (or multiple dimensions) of severity stratifications will yield more desirable clinical and analytical properties. Improved clinical and research descriptions that embody more specific details of a given pathology (rather than the simple binary case/control distinctions often made in clinical research) will undoubtedly be more sensitive and lead to more insightful research discoveries.

The current report should be considered a preliminary attempt to characterize the relative contributions of multiple medical and psychological pathologies to health-related quality of life in a non–cohort-specific sample of postdeployed Veterans with complex medical conditions. Future research that considers a broader range of functional health and quality of life indices in a larger sample (and perhaps with a longitudinal design) will be invaluable in illuminating the potential influences that war-related pathologies such as depression, PTSD, TBI, and CMI cluster problems have on Veterans' livelihood and inform better treatment approaches.

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Author Contributions:
Study concept and design: T. Sheng, M. M. Adamson, J. W. Ashford.
Acquisition of data: T. Sheng, J. Y. Kong, L. M. Kinoshita, J. K. Fairchild, J. J. Cheng.
Analysis and interpretation of data: T. Sheng, J. A. Yesavage, D. A. Helmer, M. J. Reinhard.
Drafting of manuscript: T. Sheng, M. M. Adamson, J. W. Ashford.
Clinical insights: J. Y. Kong, L. M. Kinoshita, J. K. Fairchild, J. J. Cheng, J. W. Ashford.
Critical revision of manuscript for important intellectual content: J. K. Fairchild, J. A. Yesavage, D. A. Helmer, M. J. Reinhard.
Study supervision: M. M. Adamson, J. W. Ashford, J. A. Yesavage.

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REFERENCES

1. Lange G, McAndrew L, Ashford JW, Reinhard M, Peterson M, Helmer DA. War Related Illness and Injury Study Center (WRIISC): a multidisciplinary translational approach to the care of Veterans with chronic multisymptom illness. Mil Med. 2013;178(7):705–7. https://dx.doi.org/10.7205/MILMED-D-13-00053
2. Committee on Gulf War and Health: Treatment for Chronic Multisymptom Illness, Board on the Health of Select Populations, Institute of Medicine of the National Academies. Gulf War and health: Treatment for chronic multisymptom illness [Internet]. Washington (DC): National Academies Press; 2013. Available from: http://www.ncbi.nlm.nih.gov/books/NBK206744/
3. Steele L. Prevalence and patterns of Gulf War illness in Kansas Veterans: Association of symptoms with characteristics of person, place, and time of military service. Am J Epidemiol. 2000;152(10):992–1002. [PMID:11092441] http://dx.doi.org/10.1093/aje/152.10.992
4. Fukuda K, Nisenbaum R, Stewart G, Thompson WW, Robin L, Washko RM, Noah DL, Barrett DH, Randall B, Herwaldt BL, Mawle AC, Reeves WC. Chronic multisymptom illness affecting Air Force Veterans of the Gulf War. JAMA. 1998;280(11):981–8. [PMID:9749480] http://dx.doi.org/10.1001/jama.280.11.981
5. Smith TC, Powell TM, Jacobson IG, Smith B, Hooper TI, Boyko EJ, Gackstetter GD. Chronic multisymptom illness: A comparison of Iraq and Afghanistan deployers with Veterans of the 1991 Gulf War. Am J Epidemiol. 2014;180(12):1176–87. [PMID:25466246] http://dx.doi.org/10.1093/aje/kwu240
6. Kelsall HL, McKenzie DP, Sim MR, Leder K, Forbes AB, Dwyer T. Physical, psychological, and functional comorbidities of multisymptom illness in Australian male Veterans of the 1991 Gulf War. Am J Epidemiol. 2009;170(8):1048–56. [PMID:19762370] http://dx.doi.org/10.1093/aje/kwp238
7. Carey ME. Analysis of wounds incurred by U.S. Army Seventh Corps personnel treated in Corps hospitals during Operation Desert Storm, February 20 to March 10, 1991. J Trauma. 1996;40(3 Suppl):S165–9. [PMID:8606402] http://dx.doi.org/10.1097/00005373-199603001-00036
8. Leedham CS, Blood CG, Newland C. A descriptive analysis of wounds among U.S. Marines treated at second-echelon facilities in the Kuwaiti theater of operations. Mil Med. 1993;158(8):508–12. [PMID:8414070]
9. Iversen AC, van Staden L, Hughes JH, Browne T, Hull L, Hall J, Greenberg N, Rona RJ, Hotopf M, Wessely S, Fear NT. The prevalence of common mental disorders and PTSD in the UK military: Using data from a clinical interview-based study. BMC Psychiatry. 2009;9(1):68. [PMID:19878538] http://dx.doi.org/10.1186/1471-244X-9-68
10. Kang HK, Natelson BH, Mahan CM, Lee KY, Murphy FM. Post-traumatic stress disorder and chronic fatigue syndrome-like illness among Gulf War Veterans: A population-based survey of 30,000 Veterans. Am J Epidemiol. 2003;157(2):141–8. [PMID:12522021] http://dx.doi.org/10.1093/aje/kwf187
11. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1995;52(12):1048–60. [PMID:7492257] http://dx.doi.org/10.1001/archpsyc.1995.03950240066012
12. Marmar CR, Schlenger W, Henn-Haase C, Qian M, Purchia E, Li M, Corry N, Williams CS, Ho CL, Horesh D, Karstoft KI, Shalev A, Kulka RA. Course of posttraumatic stress disorder 40 years after the Vietnam War: Findings from the National Vietnam Veterans Longitudinal Study. JAMA Psychiatry. 2015;72(9):875–81. [PMID:26201054] http://dx.doi.org/10.1001/jamapsychiatry.2015.0803
13. Schnurr PP, Spiro A 3rd. Combat exposure, posttraumatic stress disorder symptoms, and health behaviors as predictors of self-reported physical health in older Veterans. J Nerv Ment Dis. 1999;187(6):353–9. [PMID:10379722] http://dx.doi.org/10.1097/00005053-199906000-00004
14. Kang HK, Mahan CM, Lee KY, Magee CA, Murphy FM. Illnesses among United States Veterans of the Gulf War: A population-based survey of 30,000 Veterans. J Occup Environ Med. 2000;42(5):491–501. [PMID:10824302]
15. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. N Engl J Med. 2008;358(5):453–63. [PMID:18234750] http://dx.doi.org/10.1056/NEJMoa072972
16. Vanderploeg RD, Belanger HG, Horner RD, Spehar AM, Powell-Cope G, Luther SL, Scott SG. Health outcomes associated with military deployment: Mild traumatic brain injury, blast, trauma, and combat associations in the Florida National Guard. Arch Phys Med Rehabil. 2012;93(11):1887–95. [PMID:22705240] http://dx.doi.org/10.1016/j.apmr.2012.05.024
17. Baker DG, Mendenhall CL, Simbartl LA, Magan LK, Steinberg JL. Relationship between posttraumatic stress disorder and self-reported physical symptoms in Persian Gulf War Veterans. Arch Intern Med. 1997;157(18):2076–8. [PMID:9382663] http://dx.doi.org/10.1001/archinte.1997.00440390062009
18. Barrett DH, Doebbeling CC, Schwartz DA, Voelker MD, Falter KH, Woolson RF, Doebbeling BN. Posttraumatic stress disorder and self-reported physical health status among U.S. military personnel serving during the Gulf War period: A population-based study. Psychosomatics. 2002;

43(3):195–205. [PMID:12075034] http://dx.doi.org/10.1176/appi.psy.43.3.195

19. Bazarian JJ, Donnelly K, Peterson DR, Warner GC, Zhu T, Zhong J. The relation between posttraumatic stress disorder and mild traumatic brain injury acquired during Operations Enduring Freedom and Iraqi Freedom. J Head Trauma Rehabil. 2013;28(1):1–12. [PMID:22647965] http://dx.doi.org/10.1097/HTR.0b013e318256d3d3
20. Cohen H, Neumann L, Haiman Y, Matar MA, Press J, Buskila D. Prevalence of post-traumatic stress disorder in fibromyalgia patients: Overlapping syndromes or post-traumatic fibromyalgia syndrome? Semin Arthritis Rheum. 2002; 32(1):38–50. [PMID:12219319] http://dx.doi.org/10.1053/sarh.2002.33719
21. Frayne SM, Chiu VY, Iqbal S, Berg EA, Laungani KJ, Cronkite RC, Pavao J, Kimerling R. Medical care needs of returning Veterans with PTSD: Their other burden. J Gen Intern Med. 2011;26(1):33–9. [PMID:20853066] http://dx.doi.org/10.1007/s11606-010-1497-4
22. Management of Concussion/mTBI Working Group. VA/DoD clinical practice guideline for management of concussion/mild traumatic brain injury. J Rehabil Res Dev. 2009;46(6):CP1–68. [PMID:20108447]
23. Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine. Definition of mild traumatic brain injury. J Head Trauma Rehabil. 1993;8(3): 86–7. http://dx.doi.org/10.1097/00001199-199309000-00010
24. Belanger HG, Kretzmer T, Vanderploeg RD, French LM. Symptom complaints following combat-related traumatic brain injury: Relationship to traumatic brain injury severity and posttraumatic stress disorder. J Int Neuropsychol Soc. 2010;16(01):194–9. [PMID:19758488] http://dx.doi.org/10.1017/S1355617709990841
25. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: Validity of a two-item depression screener. Med Care. 2003;41(11):1284–92. [PMID:14583691] http://dx.doi.org/10.1097/01.MLR.0000093487.78664.3C
26. Li C, Friedman B, Conwell Y, Fiscella K. Validity of the Patient Health Questionnaire 2 (PHQ-2) in identifying major depression in older people. J Am Geriatr Soc. 2007; 55(4):596–602. [PMID:17397440] http://dx.doi.org/10.1111/j.1532-5415.2007.01103.x
27. Corson K, Gerrity MS, Dobscha SK. Screening for depression and suicidality in a VA primary care setting: 2 items are better than 1 item. Am J Manag Care. 2004;10(11 Pt 2): 839–45. [PMID:15609737]
28. Orsillo SM. Measures for acute stress disorder and posttraumatic stress disorder. In: Antony MM, Orsillo SM, Roemer L, eds. Practitioner's guide to empirically based measures of anxiety. New York (NY): Kluwer Academic; 2001. p. 255–307. Available from: http://link.springer.com/chapter/10.1007/0-306-47628-2_20
29. Wilkins KC, Lang AJ, Norman SB. Synthesis of the psychometric properties of the PTSD checklist (PCL) military, civilian, and specific versions. Depress Anxiety. 2011; 28(7):596–606. [PMID:21681864] http://dx.doi.org/10.1002/da.20837
30. Blanchard EB, Jones-Alexander J, Buckley TC, Forneris CA. Psychometric properties of the PTSD Checklist (PCL). Behav Res Ther. 1996;34(8):669–73. [PMID:8870294] http://dx.doi.org/10.1016/0005-7967(96)00033-2
31. Kazis LE, Miller DR, Clark JA, Skinner KM, Lee A, Ren XS, Spiro A 3rd, Rogers WH, Ware JE Jr. Improving the response choices on the veterans SF-36 Health Survey role functioning scales: Results from the Veterans Health Study. J Ambul Care Manage. 2004;27(3):263–80. [PMID:15287216] http://dx.doi.org/10.1097/00004479-200407000-00010
32. U.S. Veterans Health Administration, Office of Performance and Quality, Center for Health Quality, Outcomes & Economic Research. Health status and outcomes of Veterans: Physical and mental component summary scores (SF-36V). 1998 National Survey of Ambulatory Care Patients, Mid-Year Executive Report. Washington (DC): Department of Veterans Affairs; 1998. 139 p.
33. Ware JE Jr, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473–83. [PMID:1593914] http://dx.doi.org/10.1097/00005650-199206000-00002
34. Bousquet J, Knani J, Dhivert H, Richard A, Chicoye A, Ware JE Jr, Michel FB. Quality of life in asthma. I. Internal consistency and validity of the SF-36 questionnaire. Am J Respir Crit Care Med. 1994;149(2 Pt 1):371–5. [PMID:8306032] http://dx.doi.org/10.1164/ajrccm.149.2.8306032
35. Campbell DG, Felker BL, Liu CF, Yano EM, Kirchner JE, Chan D, Rubenstein LV, Chaney EF. Prevalence of depression-PTSD comorbidity: Implications for clinical practice guidelines and primary care-based interventions. J Gen Intern Med. 2007;22(6):711–8. [PMID:17503104] http://dx.doi.org/10.1007/s11606-006-0101-4
36. Gerrity MS, Corson K, Dobscha SK. Screening for posttraumatic stress disorder in VA primary care patients with depression symptoms. J Gen Intern Med. 2007;22(9): 1321–4. [PMID:17634781] http://dx.doi.org/10.1007/s11606-007-0290-5
37. Karstoft KI, Andersen SB, Bertelsen M, Madsen T. Diagnostic accuracy of the Posttraumatic Stress Disorder Checklist-Civilian Version in a representative military sample. Psychol Assess. 2014;26(1):321–5. [PMID:24188155] http://dx.doi.org/10.1037/a0034889

38. Keen SM, Kutter CJ, Niles BL, Krinsley KE. Psychometric properties of PTSD checklist in sample of male Veterans. J Rehabil Res Dev. 2008;45(3):465–74. [PMID:18629754] http://dx.doi.org/10.1682/JRRD.2007.09.0138
39. Kang HK, Li B, Mahan CM, Eisen SA, Engel CC. Health of US Veterans of 1991 Gulf War: A follow-up survey in 10 years. J Occup Environ Med. 2009;51(4):401–10. [PMID:19322107]
40. Asnaani A, Reddy MK, Shea MT. The impact of PTSD symptoms on physical and mental health functioning in returning Veterans. J Anxiety Disord. 2014;28(3):310–7. [PMID:24647406] http://dx.doi.org/10.1016/j.janxdis.2014.01.005
41. Lippa SM, Fonda JR, Fortier CB, Amick MA, Kenna A, Milberg WP, McGlinchey RE. Deployment-related psychiatric and behavioral conditions and their association with functional disability in OEF/OIF/OND Veterans. J Trauma Stress. 2015;28(1):25–33. [PMID:25703936] http://dx.doi.org/10.1002/jts.21979
42. Hoge CW, Terhakopian A, Castro CA, Messer SC, Engel CC. Association of posttraumatic stress disorder with somatic symptoms, health care visits, and absenteeism among Iraq War Veterans. Am J Psychiatry. 2007;164(1): 150–3. [PMID:17202557] http://dx.doi.org/10.1176/ajp.2007.164.1.150
43. Findler M, Cantor J, Haddad L, Gordon W, Ashman T. The reliability and validity of the SF-36 Health Survey Questionnaire for use with individuals with traumatic brain injury. Brain Inj. 2001;15(8):715–23. [PMID:11485611] http://dx.doi.org/10.1080/02699050010013941
44. MacKenzie EJ, McCarthy ML, Ditunno JF, Forrester-Staz C, Gruen GS, Marion DW, Schwab WC; Pennsylvania Study Group on Functional Outcomes Following Trauma. Using the SF-36 for characterizing outcome after multiple trauma involving head injury. J Trauma. 2002;52(3):527–34. [PMID:11901330] http://dx.doi.org/10.1097/00005373-200203000-00018
45. Blanchard MS, Eisen SA, Alpern R, Karlinsky J, Toomey R, Reda DJ, Murphy FM, Jackson LW, Kang HK. Chronic multisymptom illness complex in Gulf War I Veterans 10 years later. Am J Epidemiol. 2006;163(1):66–75. [PMID:16293719] http://dx.doi.org/10.1093/aje/kwj008
46. Michaels AJ, Michaels CE, Moon CH, Smith JS, Zimmerman MA, Taheri PA, Peterson C. Posttraumatic stress disorder after injury: Impact on general health outcome and early risk assessment. J Trauma. 1999;47(3):460–6, discussion 466–7. [PMID:10498298] http://dx.doi.org/10.1097/00005373-199909000-00005
47. Pietrzak RH, Johnson DC, Goldstein MB, Malley JC, Southwick SM. Posttraumatic stress disorder mediates the relationship between mild traumatic brain injury and health and psychosocial functioning in Veterans of Operations Enduring Freedom and Iraqi Freedom. J Nerv Ment Dis. 2009;197(10):748–53. [PMID:19829203] http://dx.doi.org/10.1097/NMD.0b013e3181b97a75
48. Carlson KF, Nelson D, Orazem RJ, Nugent S, Cifu DX, Sayer NA. Psychiatric diagnoses among Iraq and Afghanistan War Veterans screened for deployment-related traumatic brain injury. J Trauma Stress. 2010;23(1):17–24. [PMID:20127725]
49. Hoge CW, Castro CA. Treatment of generalized war-related health concerns: Placing TBI and PTSD in context. JAMA. 2014;312(16):1685–6. [PMID:25335151] http://dx.doi.org/10.1001/jama.2014.6670
50. Vasterling JJ, Verfaellie M, Sullivan KD. Mild traumatic brain injury and posttraumatic stress disorder in returning Veterans: Perspectives from cognitive neuroscience. Clin Psychol Rev. 2009;29(8):674–84. [PMID:19744760] http://dx.doi.org/10.1016/j.cpr.2009.08.004
51. Gironda RJ, Clark ME, Ruff RL, Chait S, Craine M, Walker R, Scholten J. Traumatic brain injury, polytrauma, and pain: Challenges and treatment strategies for the polytrauma rehabilitation. Rehabil Psychol. 2009;54(3):247–58. [PMID:19702423] http://dx.doi.org/10.1037/a0016906
52. Walker RL, Clark ME, Sanders SH. The "Postdeployment Multi-Symptom Disorder": An emerging syndrome in need of a new treatment paradigm. Psychol Serv. 2010;7(3): 136–47. http://dx.doi.org/10.1037/a0019684
53. Engel CC Jr, Liu X, McCarthy BD, Miller RF, Ursano R. Relationship of physical symptoms to posttraumatic stress disorder among Veterans seeking care for Gulf War-related health concerns. Psychosom Med. 2000;62(6):739–45. [PMID:11138991] http://dx.doi.org/10.1097/00006842-200011000-00001
54. Wolfe J, Proctor SP, Erickson DJ, Heeren T, Friedman MJ, Huang MT, Sutker PB, Vasterling JJ, White RF. Relationship of psychiatric status to Gulf War Veterans' health problems. Psychosom Med. 1999;61(4):532–40. [PMID:10443762] http://dx.doi.org/10.1097/00006842-199907000-00018
55. Miller CS, Ashford NA. Chronic multisystem illness among Gulf War Veterans. JAMA. 1999;282(4):328–9. [PMID:10432028]
56. Nisenbaum R, Barrett DH, Reyes M, Reeves WC. Deployment stressors and a chronic multisymptom illness among Gulf War Veterans. J Nerv Ment Dis. 2000;188(5):259–66. [PMID:10830562] http://dx.doi.org/10.1097/00005053-200005000-00002
57. Wolfe J, Proctor SP, Erickson DJ, Hu H. Risk factors for multisymptom illness in US Army Veterans of the Gulf War. J Occup Environ Med. 2002;44(3):271–81. [PMID:11911029]

58. Petrie KJ, Moss-Morris R, Grey C, Shaw M. The relationship of negative affect and perceived sensitivity to symptom reporting following vaccination. Br J Health Psychol. 2004;9(Pt 1):101–11. [PMID:15006204] http://dx.doi.org/10.1348/135910704322778759
59. Hawkley LC, Cacioppo JT. Loneliness and pathways to disease. Brain Behav Immun. 2003;17(1 Suppl 1):S98–105. [PMID:12615193] http://dx.doi.org/10.1016/S0889-1591(02)00073-9
60. Uchino BN, Cacioppo JT, Kiecolt-Glaser JK. The relationship between social support and physiological processes: A review with emphasis on underlying mechanisms and implications for health. Psychol Bull. 1996;119(3):488–531. [PMID:8668748] http://dx.doi.org/10.1037/0033-2909.119.3.488
61. Frueh BC, Gold PB, de Arellano MA. Symptom overreporting in combat Veterans evaluated for PTSD: Differentiation on the basis of compensation seeking status. J Pers Assess. 1997;68(2):369–84. [PMID:9107014] http://dx.doi.org/10.1207/s15327752jpa6802_8

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